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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/752,857	12/28/2000	G. Patrick Stahly	13001US01	1453

7590 07/01/2002

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EXAMINER
GAKH, YELENA G

ART UNIT	PAPER NUMBER
1743	3

DATE MAILED: 07/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

MFB

Office Action Summary	Application No.	Applicant(s)	
	09/752,857	STAHLY ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1743	

-- The MAILING DATE of this communication appears on th cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. No disclosure is given in the specification on how to provide data on biological activity or bioavailability of solidified samples. No examples are provided of how such analysis can be done. No references disclosing this type of analysis, are cited. The specification does not enable anyone of ordinary skill to conduct the analytical step recited in claim 41.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites, "a method of searching for possible forms of a sample". What does it mean? Such phraseology makes the claim unclear, indefinite, and renders it to a non-statutory subject matter. The examiner interprets this claim as "a method for detecting possible forms" in order to examine the pending claims on merits. The correction of the claim language is required.

Claims 1 and 34 recite "forms" of a sample, which is an indefinite term, since it is not clear, which characteristics of the sample it defines. Are these physical forms, chemical forms, mechanical forms, shapes, etc.? Such terminology renders the claims unclear and indefinite. Claims 1 and 34 further recite classification of said form, however, it is not clear, what type of classification is meant here.

Claim 12 is unclear. First, no word "placing" was used in the parent claim, which recited a "disposing" step; the same terminology should be used in the dependent claim. Second, it is not clear, how the sample can be placed into the receptacle, which is a block or a sheet with holes. Does it mean that the sample is placed in the holes?

Claim 21 recites "at least one different form of the sample". How is it possible? How one form may be different? Different from what?

Claims 26 and 27 are unclear. What does it mean that the centrifuging is sufficient to facilitate in-situ analysis or to provide environmental variation? Does it mean in the first case that centrifuging is long enough to obtain enough solidified sample for the analysis, or it means something else? In the second case it is not clear, what kind of "environmental variations" are meant here, and how centrifuging can provide them.

Claim 53 recites "a method of screening a sample". It is not clear, how it is possible to screen just one sample. What is it screening for? Further it recites, "said at least one form ... indicative of the generated form". Both of these limitations do not have an antecedent bases in this claim. Neither "at least one form" or "generated form" were recited previously in the claim.

Claim 54 is incomplete. It is not clear, "said centrifuging step at least partially" what?

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

4. **Claims 1-3, 6-9, 11, 13, 14, 20, 21, 34-37, 39, 40, 42, 43, 45, 50-52** are rejected under 35 U.S.C. 102(e) as being anticipated by Hol et al. (US 6,267,935 B1).

Hol teaches a method for screening different crystalline and amorphous forms of biologically active macromolecules placing solutions in a plurality of receptacles and crystallizing them by different techniques, including evaporation of the solvent with following monitoring of the process by stereomicroscope and further by X-ray diffraction analysis. The conditions are varied to obtain crystal forms instead of amorphous forms for some of the compounds. "In the technique of capillary crystallization, layers of sample solution and crystallization solution can be deposited in a capillary 0.5-1.0 mm in diameter, either with an air space between the solutions or with a direct liquid--liquid interface. Crystallization occurs by vapor diffusion or liquid--liquid diffusion inside the capillary" (col. 10, lines 51-56).

5. **Claims 1, 2, 8, 9, 11, 13, 17, 18, 20, 34, 36, 39, 40, 42, 45, 48, and 49** are rejected under 35 U.S.C. 102(b) as being anticipated by Plaas-Link (US 5,009,861).

Plaas-Link discloses a method of determining crystal forms of samples using a crystallization apparatus to crystallize e.g. biologically active proteins from solutions inside a glass capillary so that "unhampered observation of the crystallization progress is made possible" (col. 4, lines 14-17) when "liquid is evaporated out of the capillary tubes" (col. 4, lines 20-22). The observation of the formation of crystals has an inherited step of classification them as crystals. A plurality of capillaries or cells is disclosed for crystallization of a plurality of protein samples.

6. **Claims 1-3, 8, 9-11, 13, 17, 18, 20, 21, 34-40, 42, 45, 48, and 49** are rejected under 35 U.S.C. 102(b) as being anticipated by Schuler et al. (US 4,295,857, IDS).

Schuler teaches a process for the crystalline precipitation of chromogenes within a capillary, i.e. determining crystalline forms of the samples. "The process involves first initiating a course of crystalline precipitation of the chromogen by initially and locally supersaturating the solution within the capillary, and thereafter evaporating the solvent at a rate and in an environment sufficient for further crystallization to proceed unimpeded by local supersaturation" (Abstract). In the Background of the Invention Schuler discloses preparation and observation of formation of several forms, crystalline, as well as amorphous, of several biologically active compounds, in capillaries by evaporating solvent with following spectroscopic analysis (columns

1 and 2). "It has been proposed to include such small amounts of substance in a solvent, fill a capillary with the resultant solution, and precipitate the substance by evaporating the solvent in the capillary". In the case of 4-aminophenazone, "this substance tends to deposit from a large number of solvents upon evaporation of the solvent not in crystalline form but as an amorphous oil. The oil obtained begins to solidify after a short period of time forming a yellow color, and a resinous hydrophobic layer is produced by which the capillary loses its absorption capacity. The yellow coloration of the substance expresses itself in a new band in the absorption spectrum and has a disturbing effect on photometric measurement due to the occurrence of high reagent blank values. If the conditions under which the solvent is evaporated are varied, for instance by applying a vacuum, it is, it is true, possible in individual cases to obtain a finely crystalline precipitation with good absorptivity" (col. 2, lines 15-33). In the Background of the Invention Schuler discusses preparation of a mixture of several components using capillaries (col. 1, lines 25-45).

7. **Claims 1, 2, 8, 9, 11, 13, 16-18, 20, 22, 23** are rejected under 35 U.S.C. 102(b) as being anticipated by JP 06095190.

JP 06095190 discloses growing an organic single crystal in a capillary by heating inserted capillary in the furnace, rotating it while evaporating the solvent and detecting and discriminating the organic single crystal by Raman diffusion spectroscopy.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. **Claims 4, 5, and 12** are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuler.

Schuler does not particularly disclose disposing the compounds in different types of receptacles, including non-capillary or subjecting at least two different samples to different conditions during solidifying step. However, in the Background of the Invention he discusses different conditions of evaporation, which affect the crystallization of the compound and its end form.

It would have been obvious for anyone of ordinary skill to vary the conditions of evaporation of solvents in a different way than disclosed by Schuler, namely by using capillaries along with other types of receptacles, because this is another way to find out the best conditions for obtaining crystalline, rather than amorphous, form of the compound, as discussed by Schuler in col. 2, lines 20-35. It would have been obvious for anyone of ordinary skill to subject at least two samples to different conditions of solidifying, which results in different crystalline forms of the compounds, because Schuler directly expressed that the condition of the evaporation strongly affects the result of crystallization.

12. **Claims 6 and** 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plaas-Link. Plaas-Link does not specifically disclose placing the same sample in a plurality of capillaries, however, "mere duplication of parts without any new and unexpected results is within the skill in the routineer in the art (see *In re Harza*, 124 USPQ 378 (CCPA 1960)).

13. **Claims 15, 17-19, 43, 44, 46, 48,** are rejected under 35 U.S.C. 103(a) as being unpatentable over Hol in view of Subbiah (US 5,200,910).

Hol does not particularly disclose synchrotron radiation as the radiation source in X-ray analysis and analyzing the sample directly in the capillary.

Subbiah teaches a method for modeling the electron density of a crystal by X-ray analysis of the crystal sample placed in the capillary tube (col. 7, lines 7-12), where X-ray radiation source is a synchrotron (col. 6, line 67).

It would have been obvious for anyone of ordinary skill to use synchrotron as a source of radiation for X-ray analysis and perform the analysis directly in the capillaries, as disclosed by Subbiah, in Hol's method, because synchrotron is a tunable X-ray source, and because performing X-ray analysis directly in the receptacle where the sample is prepared is convenient and more accurate way of collecting X-ray data.

14. **Claims 16, 38 and 47** are rejected under 35 U.S.C. 103(a) as being unpatentable over any of Hol, Plaas-Link or Schuler in view of Gu et al. (J. Pharmac. Sci., IDS).

Hol, Plaas-Link or Schuler do not teach Raman spectroscopic analysis in their methods or discuss polymorphic forms of the compounds.

Gu teaches characterization of polymorphic forms of the sample using FT Raman spectroscopy.

It would have been obvious for anyone of ordinary skill to use FT Raman scattering analysis instead of X-ray analysis, especially in the case of polymorphic compounds, as taught by Gu, in Hol's, Plaas-Link's or Schuler' method, because as Gu emphasizes, "FT-Raman technique is more suitable for studying certain polymorphs" (Introduction).

15. **Claims 24-33, and 53** are rejected under 35 U.S.C. 103(a) as being unpatentable over any of Hol, Plaas-Link or Schuler in view of Kajola (Acta Chem. Scand., Abstract).

Hol, Plaas-Link or Schuler do not disclose centrifuging the samples in capillaries during crystallization under vacuum.

Kajola discloses "reaction tubes [which] are made by drawing out 10-mm. glass tubing to 2 mm. diam. In these tubes the reagents are mixed and the reaction is carried out in the sealed tube. Drawing the end of the reaction tube to a fine capillary produces an effective micro-filter

Hol, Plaas-Link or Schuler do not disclose centrifuging the samples in capillaries during crystallization under vacuum.

Kajola discloses "reaction tubes [which] are made by drawing out 10-mm. glass tubing to 2 mm. diam. In these tubes the reagents are mixed and the reaction is carried out in the sealed tube. Drawing the end of the reaction tube to a fine capillary produces an effective micro-filter and the mother liquor can be centrifuged through this capillary; any crystals are left in the tube" (Abstract).

It would have been obvious for anyone of ordinary skill to use centrifugation in Hol's, Plaas-Link's or Schuler's process of crystallization of the samples, as taught by Kajola, because Kajola teaches effectiveness of using centrifugation in separating crystal from the solvent in a capillary.

16. **Claims 55 and 56** are rejected under 35 U.S.C. 103(a) as being unpatentable over any of Hol, Plaas-Link or Schuler in view of Kajola, as applied to claims 24-33, and 53 above, and further in view of Bringi et al. (US 4,060,646).

Hol, Plaas-Link or Schuler in view of Kajola does not specifically disclose centrifuging under vacuum.

Bringi teaches fractional crystallization of food fat, wherein "separation of the crystallized fat from the mother liquor may be effected by filtration or centrifugation and accompanied with the application of vacuum or pressure".

It would have been obvious for anyone of ordinary skill to apply vacuum during centrifugation disclosed by Bringi in Hol, Plaas-Link or Schuler/Kajola's method, because this increases the effectiveness of the centrifugation.

Conclusion

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. *Kaye et al. (US 5,614,726)* teach a method using Raman scattering of capillary tube contents.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (703) 306-5906. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (703) 308-4037. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9310 for regular communications and (703) 872-9311 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

YG
June 21, 2002

Jill Warden
Supervisory Patent Examiner
Technology Center 1700